Journal of **N**onlinear **A**nalysis and **O**ptimization
Vol. 15, Issue. 1, No.1 : 2024
ISSN : **1906-9685**

AN INSIGHT INTO CHIKUNGUNYA VIRUS INFECTION

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Introduction

Chikungunya is an illness characterized by debilitation, transmitted via mosquitoes, and caused by the chikungunya virus (CHIKV). It was first identified in Tanzania in 1953 (Lumsden 1955; Robinson 1955; Ross 1956). Chikungunya term originated from the Makonde language and translates to 'to be contorted,' describing the bent posture of individuals experiencing intense joint pain. Chikungunya has been classified into 4 lineages: West African, Asian lineage, East Central South African (ECSA), and Indian Ocean lineage (IOL) (Volk et al., 2010). It belongs to the genus *Togaviridae* of the alphavirus family. Alphaviruses are divided into two distinct groups: Old World alphaviruses, which encompass Semliki Forest virus, Chikungunya, and Ross River virus leading to arthralgia; and New World alphaviruses, such as the Venezuelan equine encephalomyelitis virus, which causes encephalitis.
Chikungunya is a self-limiting disease that typically resolves on its own and is characterized by a low mortality rate. Its genome comprises approximately 11.8 kb of single-stranded RNA. The C-E3-E2-6k-E1encodes for structural proteins and nsP1-nsP2-nsP3-nsP4 codes for non-structural proteins. Capsid proteins form icosahedral nucleocapsid whereas E1 and E2 form surface glycoproteins which facilitate the attachment and entry into the cell surface, respectively (Verma et al., 2021).

Symptoms

The incubation period of the virus is 4-7 days followed by which symptoms appear. The symptoms of chikungunya overlap with Dengue and Zika virus. Typical clinical symptoms include fever, joint pain, headache, rashes, rigors, joint pain, vomiting, and myalgia. It's noteworthy that polyarthralgia can endure for an extended period (Suhrbier et al., 2012; Seymour et al., 2013).

Transmission

Chikungunya is caused by the bite of the Aedes mosquito primarily *Aedes aegypti* which is confined to the tropics and *Aedes albopictus* which dominates in the temperate region. Originally, *Aedes aegypti* was known as the primary carrier for the virus transmission. However, a mutation known as A226E in the E1 protein subsequently enhanced the virus's ability to replicate in *Aedes albopictus* (Bonilauri et al., 2008; Sang et al., 2008; Verma et al. 2021).

Pathology of Chikungunya

Chikungunya disease has been characterised into Acute and Chronic phases. The acute phase is defined as the first 14 days following the onset of infection. It is further subdivided into the viral phase (0-5 days post-infection) and the convalescent phase (5-14 days post-infection). On the contrary, the chronic phase appears on the persistence of clinical symptoms post 3 months of infection. It is characterised by debilitating joint pain which can last from months to years. Elderly individuals have an increased risk of progression of disease (Chaaitanya et al., 2011; Suhrbier et al., 2012; Seymour et al., 2013).

Tropism

Virus tropism is the term used to describe the virus's capability to infect a specific cell or tissue. It depends on the presence of receptors on the cell surface for the viral attachment. The binding of CHIKV to cells is facilitated by the E2 protein of the virus (Verma et al., 2021). It has strong tropism towards the fibroblast cells and macrophages/monocytes. Apart from this, in various tissue culture experiments replication of the virus was found in adherent cells as well such as epithelial and endothelial cells.

Epidemiology

After the first outbreak of Chikungunya that occurred in Tanzania, numerous cases of the epidemic have been reported worldwide. West African countries have been dominated by West African strains and ECSA strains have expanded outside Africa including Asia. In 1999-2000, a large outbreak was reported in the Democratic Republic of Congo. In 2004, an ECSA strain remerged during a devastating outbreak in Kenya. Subsequently, the virus extended its geographical presence to various islands in the Indian Ocean and regions of Southeast Asia. Another major outbreak took place on the French island of Reunion in 2005 followed by Italy in 2007 and the Pacific Island region of New Caledonia in 2011. Early in 2012, islands in Oceania were also victimized by CHIKV outbreaks (Schuffenecker et al., 2006; Paquet et al., 2006). Further in 2013, the CHIKV Asian genotype inflicted the population of Caribbean and America. Apart from this Sudan also witnessed the epidemic in 2019 and at beginning of 2020 new cases were also reported in Brazil and Columbia (Kendrick et al., 2014).

Life cycle of CHIKV

In alphaviruses, envelope 1 and 2 proteins are recognized for their pivotal role in attaching the virus to host cells. The E1 and E2 glycoproteins pair and form a hetero-trimeric spike that coats the virus surface. The presence of cholesterol in the plasma membrane of host cells aids in facilitating the endocytic process into distinct compartments (Kielian and Rey, 2006). In the case of Chikungunya, the E2 glycoprotein binds to the receptor on the cell surface and enters through either clathrin-mediated or clathrin-independent endocytosis (Bernard et al., 2010). After getting directed to the endosomes, dissociation of heterotrimer occurs due to an acidic environment followed by confirmation change of E1 that facilitates the fusion of host membrane and virus. Subsequently, the nucleocapsid is liberated into the cytoplasm, triggering the release of genomic RNA. Following this, non-structural proteins undergo translation and subsequently autoproteolytically cleave into nsp123 and nsp4. These proteins thereafter with the help of other host proteins generate negatively stranded RNA which acts as a template for positive strand RNA. Thereafter, structural proteins are generated and further autoproteolytically cleaved to capsid(C) and E2-6K-E1 polyprotein (Voss et al., 2010). The polyprotein is subsequently inserted into the endoplasmic reticulum and directed towards the plasma membrane via the Golgi. Concurrently, it undergoes post-translational modification, leading to the formation of the mature E2-E1 heterodimer. In the end, capsid proteins (C) interact with genomic RNA, forming nucleocapsids that are transported to the plasma membrane. Subsequently, they are budded out with the host membrane to release the mature virion (Voss et al., 2010; Li et al., 2010; Weber et al., 2017).

Diagnosis of CHIKV

Laboratory diagnostic methods include viral isolation, molecular techniques such as RT PCR and real-time PCR as well as serological assays which include ELISA techniques for detection of IgM and IgG antibodies (Verma et al., 2021). The test used for viral detection depends primarily on the time of sample collection. Viral isolation is suitable for the samples collected before 7 days of infection and cytopathic effects can be visualised on numerous cell lines such as Vero and HeLa cells which appear in 3 days. Immunofluorescence can also be used for visualisation of the virus. However, virus isolation is a long procedure and requires a BSL3 laboratory. Molecular techniques such as PCR, which is a rapid and sensitive method, are also valid till the 7th day after the onset of symptoms (Verma AK et al., 2016). Among the serological tests which include IgM and IgG ELISA and immunochromatic tests

can be employed from 5th day after the symptom onset till a few weeks (Thein et al., 1992; Kumarasamy et al., 2006; Kr Verma A et al., 2014; Verma A, et al., 2016).

Immune response to Chikungunya

Macrophages, Dendritic cells, and NK cells are the key players in the innate immune response against viruses. This is succeeded by adaptive immune response which comprises of B and T cells. The acute phase of chikungunya is marked by an elevation in the level of NK cells. Moreover, CHIKV-associated joint pathology is attributed to monocytes and macrophages. In fact, macrophages act as a cellular hub for the persistence of chikungunya infection in the chronic phase (Sam et al., 2015). Anti-chikungunya IgG antibodies have been identified during the convalescent phase of Chikungunya in humans (Verma et al., 2021). Envelope protein E2 is known to be the prime epitope for the antibody. Amongst the T cells, CD8 Tc cell marks the early stage of chikungunya infection and CD4 Th cells play a chief role in triggering further immune cells via chemokines and cytokines production. In Chikungunya-infected individuals, there is a significant increase in the levels of cytokines such as I IFNγ, IL-8, IL-10, IFNα, IL-6, and the anaphylatoxin C5a (Ng et al., 2009; Hoarau et al., 2010; Chow et al., 2011).

Treatment

To date, no specific treatment exists for chikungunya. Upon onset of symptoms present treatment focuses on alleviating the severity of symptoms which involves antipyretics, analgesics, and NSAIDs. Apart from this, patients are recommended to take plenty of fluids and extensive bed rest. The use of aspirin should be avoided in chikungunya-infected patients. There exists no commercial vaccine for chikungunya. The first chikungunya vaccine employed formalin inactivated virus which was developed by the US military. But it was discontinued later. Though many attempts have been made to develop attenuated vaccines, virus-like particles (VLP) based vaccines, recombinant antigen, and DNA vaccines however due to unprecedented outbreaks of chikungunya, the efficacy of the CHIK vaccine could not cross phase III clinical trials which is a prerequisite for approval by US FDA. Recently a vaccine has been developed by French biotech company Valneva and is under phase I trial. This vaccine is a live attenuated form of the chikungunya virus (WHO, 2008; van Genderen et al., 2016).

Prevention and Control

The best possible way to prevent chikungunya is to wipe out the breeding grounds of mosquitoes which include stagnant water bodies such as flowerpots, coolers, birdbaths, rainwater barrels, ponds marshes, etc. Water should be replaced on a weekly basis on the sources of standing water sources. Several plants such as lavender and mint also help in getting rid of mosquitoes. Insect repellent should be used such as mosquito coils or insect vaporizers. The use of mosquito nets should be promoted to reduce indoor biting (Tournebize et al., 2009).

Conclusion

Chikungunya has been one of the neglected diseases until the recent epidemic. The main reason for this could be attributed to its symptoms which overlap with Dengue and Zika virus. Numerous studies have been done on the pathogenesis of the virus, chronic infection, and role of immune response in Chikungunya but still lot more mechanisms need to be addressed. As of now, there is no developed antiviral drug or vaccine for this virus, but research is ongoing to explore potential vaccine candidates.

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